SYNTHESIS AND SOME TRANSFORMATIONS OF PYRROLES WITH ALIPHATIC ACYL SUBSTITUENTS

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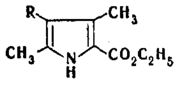
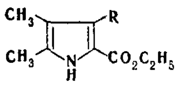
A number of higher aliphatic pyrryl ketones were synthesized. It is shown that a carbethoxy group in the 5 position of the pyrrole ring relatively weakly deactivates the 3 position of the ring to electrophilic attack during Friedel–Crafts acylation but hinders this reaction considerably when it is in the adjacent 4 position. The oxidation of the α-methyl group in a series of pyrryl ketones and the corresponding alcohols was studied.

Higher aliphatic pyrryl ketones are of considerable interest both from the point of view of the possibility of their use for the synthesis of porphyrins related to heme *a* [1] and in connection with their potential pharmacological action [2]. One of the most promising methods for the preparation of these compounds is Friedel–Crafts acylation of α- and β-unsubstituted pyrroles.

In the present investigation, we studied the effect of an α-carbethoxy group on the ease of introduction of an acyl substituent into the 3 and 4 positions of the pyrrole ring. 2,4-Dimethyl-5-carbethoxypyrrole (Ia) and 2,3-dimethyl-5-carbethoxypyrrole (IIa) were selected as the starting compounds. The reaction was carried out in dichloroethane in the presence of anhydrous aluminum chloride. The acylation of pyrrole Ia with palmityl chloride proceeded successfully even at 20° C, and 2,4-dimethyl-3-(1-oxohexadecyl)-5-carbethoxypyrrole (Ic) was obtained in practically quantitative yield. Pyrrole Ia was also readily acylated with propionyl chloride and stearyl chloride to give Ib and Id in 92.5 and 97.5% yield, respectively.



I



II

a $R=H$; b $R=COC_2H_5$; c $R=COC_{15}H_{31}$; d $R=COC_{17}H_{35}$

To a certain degree, the results obtained in the acylation of 2,3-dimethyl-5-carbethoxypyrrole (IIa) were unexpected. In this case, the yield of 2,3-dimethyl-4-(1-oxohexadecyl)-5-carbethoxypyrrole (IIc) was only 34%. The yield was not raised substantially by increasing the amount of catalyst or by heating. We were able to obtain pyrrole IIc in higher yield (62%) only by replacing dichloroethane by another solvent – nitromethane – in which, as it turned out, the complex of the starting pyrrole with aluminum chloride is more soluble. The results are evidence that in the Friedel–Crafts acylation of pyrroles, the α-carbethoxyl group markedly increases the reactivity of the adjacent β position and only slightly deactivates the more distant β' position.

The important step in the conversion of pyrroles to dipyrrylmethanes – intermediates in the synthesis of porphyrins – is oxidation of the α-methyl group with lead tetraacetate or some other oxidizing agent. The presence of electron-acceptor substituents hinders this reaction. It is known that 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole cannot be oxidized with lead tetraacetate [3]. Having in view the strong deactivating effect of the acyl group, we undertook the reduction of the carbonyl group in Ib and Ic with sodium borohydride. As a result, we obtained the corresponding alcohols (IIIa and IIIb). The hydroxyl group in

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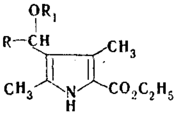
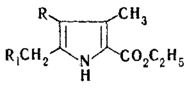


III

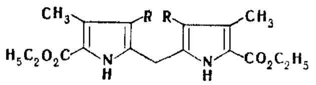


IV

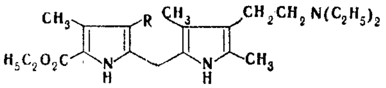
III a $R=C_2H_5$, $R_1=H$; b $R=C_{15}H_{31}$, $R_1=H$; c $R=C_{15}H_{31}$, $R_1=COCH_3$;

IV a $R=COC_{17}H_{35}$, $R_1=OCH_3$; b $R=COC_{15}H_{31}$, $R_1=Cl$

pyrrole IIIb was protected by means of acetic anhydride. The resulting IIIc was then oxidized with lead tetraacetate to the corresponding α-acetoxymethyl derivative. In the course of subsequent investigations, we found that the pyrryl ketones can be directly oxidized with lead tetraacetate. We were able to obtain 2-acetoxymethyl-4-methyl-3-(1-oxooctadecyl)-5-carbethoxypyrrole. This difference in the reactivities of pyrryl ketones and 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole attests to the activating effect of a large alkyl substituent. Heating of the α-acetoxymethyl derivative in methanol with a small amount of hydrobromic acid converted it to 2-methoxymethyl-4-methyl-3-(1-oxooctadecyl)-5-carbethoxypyrrole (IVa), which could not be used for the dipyrrylmethane condensation [4]. A symmetrical dipyrrylmethane (V) was formed when this reaction was carried out with a large amount of HBr.



V



VI

V $R=COC_{17}H_{35}$ VI $R=COC_{15}H_{31}$

We therefore abandoned our research with α-acetoxymethyl-substituted derivatives and turned to the corresponding α-chloromethylpyrroles. Treatment of pyrrole Ic with sulfuryl chloride in o-dichlorobenzene at 50° gave 2-chloromethyl-4-methyl-3-(1-oxohexadecyl)-5-carbethoxypyrrole (IVb). The latter was introduced into condensation with 2,4-dimethyl-3-(2-diethylaminoethyl)pyrrole in chloroform containing triethylamine [5]. The resulting 4,3',5'-trimethyl-3-(1-oxohexadecyl)-4'-(2-diethylaminoethyl)-5-carbethoxydipyrrylmethane (VI) can be used for model syntheses of porphyrin *a*.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Perkin Elmer 257 spectrometer.

Acylation. A 1.2-mole sample of the acid chloride was added dropwise to an ice-cooled stirred suspension of 1 mole of the pyrrole and 1.1 mole of anhydrous aluminum chloride, and the mixture was then allowed to stand at room temperature for 24 h. The solvent was removed in vacuo, finely ground ice was added to the residue, and the mixture was acidified to pH 1 with hydrochloric acid. The pyrrole was extracted with chloroform, and the extract was washed with water until it was neutral. The chloroform was removed by distillation, and the residue was recrystallized from isopropyl alcohol. The reaction was carried out similarly (see Table 1) when nitromethane was used as the solvent.

2,4-Dimethyl-3-(1-hydroxyhexadecyl)-5-carbethoxypyrrole (IIIb). A solution of 0.3 g of sodium borohydride in 10 ml of 50% aqueous ethanol containing two drops of 2 N sodium carbonate solution was added to a solution of 1.76 g of pyrrole Ic in 50 ml of ethanol, and the mixture was stirred at 50° for 4 h. The precipitate was removed by filtration, and the solution was evaporated to one third its original volume. The resulting precipitate was removed by filtration and dried to give 1.62 g (97%) of IIIb with mp 71-72.5° [from petroleum ether–benzene (1:1)]. IR spectrum: 3280 (NH), 1675 cm^{-1} ($COOC_2H_5$). Found: C 73.91; H 10.69; N 3.84%. $C_{25}H_{45}NO_3$. Calculated: C 73.67; H 11.13; N 3.44%.

2,4-Dimethyl-3-(1-hydroxypropyl)-5-carbethoxypyrrole (IIIa). This compound was obtained in 82% yield from Ia via a method similar to that used to prepare IIIb and had mp 88-89° (from petroleum ether). IR spectrum: 3300 (NH), 1660 cm^{-1} ($COOC_2H_5$). Found: C 64.24; H 8.50; N 6.09%. $C_{12}H_{19}NO_3$. Calculated: C 63.96; H 8.50; N 6.22%.

2,4-Dimethyl-3-(1-acetoxyhexadecyl)-5-carbethoxypyrrole (IIIc). A 0.83-g sample of IIIb was dissolved by heating in 8 ml of dry pyridine, 1 ml of acetic anhydride was added, and the mixture was stirred at 20° for 12 h. The mixture was then diluted with water, and the precipitate was removed by filtration,

TABLE 1. β-Acylpyrroles

Compound	Reaction time, h	mp, °C	IR spectrum, cm^{-1}			Empirical formula	Found, %			Calc., %			Yield, %
			ν_{NH}	$\nu_{C=O}$ (ester)	$\nu_{C=O}$ (ketone)		C	H	N	C	H	N	
Ib	24	139—140[b]	3280	1660	1650	$C_{12}H_{17}NO_3$	—	—	—	—	—	—	92,5
Ic[c]	18	94—94,5	3280	1665	1650	$C_{25}H_{43}NO_3$	74,47	11,00	3,67	74,04	10,69	3,47	98,5
Id	20	95—96	3280	1655	1645	$C_{27}H_{47}NO_3$	74,76	11,00	3,27	74,77	10,93	3,23	97,5
IIc[d]	24	92,5—93	3300	1660	1655sh.	$C_{25}H_{43}NO_3$	73,90	10,62	3,89	74,04	10,69	3,47	34

[a] The reaction temperature was 20°. [b] According to the data in [6], mp 140°. [c] When the reaction was carried out without a solvent, this pyrrole was obtained in 85% yield and had mp 91-92° [7]. [d] When this reaction was carried out in nitromethane, the yield of pyrrole was 62%.

washed with water, and recrystallized from hexane to give 1.12 g (96.5%) of a product with mp 62-63°. IR spectrum: 3280 (NH), 1727 ($OCOCH_3$), 1665 cm^{-1} ($COOC_2H_5$). Found: C 72.45; H 10.97; N 3.42%. $C_{27}H_{47}NO_4$. Calculated: C 72.12; H 10.54; N 3.12%.

2-Methoxymethyl-4-methyl-3-(1-oxooctadecyl)-5-carbethoxypyrrole (IVa). A 2.15-g sample of lead tetraacetate was added in portions to a solution of 1.67 g of Id in 25 ml of absolute benzene at 60°, and the mixture was heated for 20 h. The lead diacetate was removed by filtration, the filtrate was vacuum evaporated, and the residue was washed with petroleum ether to give 1.61 g (84.5%) of 2-acetoxymethyl-4-methyl-3-(1-oxooctadecyl)-5-carbethoxypyrrole with mp 84-85° [from petroleum ether–benzene (1:1)]. IR spectrum: 3275 (NH), 1742 (acetoxymethyl C=O), 1663-1667 cm^{-1} (ketone and ester C=O). A 0.5-g sample of the pyrrole was refluxed for 4 h in 25 ml of methanol containing 0.5 ml of 40% hydrobromic acid. The solution was cooled, and the precipitated crystals were removed by filtration and recrystallized from methanol to give 0.4 g (85%) of IVa with mp 94-96°. IR spectrum: 3285 (NH), 1660 ($COOC_2H_5$), 1650 cm^{-1} (ketone C=O). Found: C 72.65; H 10.92; N 3.01%. $C_{28}H_{49}NO_4$. Calculated: C 72.52; H 10.65; N 3.02%.

4,4'-Dimethyl-3,3'-di(1-oxooctadecyl)-5,5'-dicarbethoxydipyrrylmethane (V). A 0.5-g sample of 2-acetoxymethyl-4-methyl-3-(1-oxooctadecyl)-5-carbethoxypyrrole was refluxed for 4 h in 25 ml of methanol and 3 ml of 40% hydrobromic acid. The mixture was then evaporated to one third of its original volume and cooled. The precipitate was removed by filtration and recrystallized from methanol to give 0.3 g (71%) of a product with mp 116-117.5°. IR spectrum: 3340 (NH), 1690 ($COOC_2H_5$), 1650 cm^{-1} (ketone C=O). Found: C 74.89; H 11.10; N 3.38%. $C_{53}H_{90}N_2O_6$. Calculated: C 74.79; H 10.66; N 3.28%.

2-Chloromethyl-4-methyl-3-(1-oxohexadecyl)-5-carbethoxypyrrole (IVb). A 0.85-ml (125%) sample of sulfuryl chloride was added slowly with stirring to a heated (50°) suspension of 3.2 g of Ic in 16 ml of anhydrous o-dichlorobenzene. The mixture was heated for 2 h and then diluted with 20 ml of petroleum ether. The resulting precipitate was separated, washed with petroleum ether, and dried to give 2.6 g (75%) of IVb with mp 99-100.5° [from ether–benzene (1:1)]. IR spectrum: 3280 (NH), 1670 ($COOC_2H_5$), 1660 cm^{-1} (C=O). Found: C 68.34; H 9.59; Cl 8.27; N 3.14%. $C_{25}H_{42}ClNO_3$. Calculated: C 68.22; H 9.62; Cl 8.06; N 3.18%.

4,3',5'-Trimethyl-3-(1-oxohexadecyl)-4'-(2-diethylaminoethyl)-5-carbethoxydipyrrylmethane (VI). A 0.56-g sample of IVb and 0.25 g of 2,4-dimethyl-3-(2-diethylaminoethyl)pyrrole in 15 ml of absolute chloroform and 0.7 ml of triethylamine were refluxed for 6 h under nitrogen. The mixture was washed with water, the chloroform was vacuum evaporated, and IV was chromatographed on aluminum oxide. The compound was eluted with chloroform, the solvent was evaporated, and the residue was triturated with petroleum ether to give 0.31 g (41.5%) of a product with mp 94-95° (from hexane). IR spectrum: 3310-3320 (NH), 1700 ($COOC_2H_5$), 1660 cm^{-1} (C=O). Found: C 74.07; H 10.68; N 6.65%. $C_{35}H_{59}N_3O_3$. Calculated: C 74.32; H 10.62; N 7.03%.

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